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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,722	07/10/2006	Rosanne M Crooke	BIOL0004USA	6604

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,722	CROOKE ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 11, 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61,65-70,72-76 and 84-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61,65-70,72-76 and 84-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *June 11, 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on June 11, 2009 has been entered.

Claims 61, 65-70, 72-76, and 84-99 are pending.

Claims 61, 65-70, 72-76, and 84-99 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Applicant's Amendment and Response filed June 11, 2009 has been considered. Rejections and/or objections not reiterated from the previous Office Action mailed May 14, 2008 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Information Disclosure Statement

Applicant's information disclosure statement (IDS) filed June 11, 2009 is

acknowledged. It is noted that the information disclosure statement lists references C04, C05, and C09-C13, which are previous Office Actions for U.S. Patent Applications. It is noted that when the instant application goes to issuance, an Office Action is not a valid publication that can be printed on the face of a printed patent. Therefore, the Office Actions have been considered, however, the Examiner has lined through the citations to prevent them from being printed on the face of the issued patent. Accordingly, the Examiner has considered the information disclosure statement filed June 11, 2009, and a signed copy is enclosed herewith.

Double Patenting

In the previous Office Action mailed May 14, 2008, claims 61, 65-70, and 72-76 were provisionally rejected under the judicially created doctrine of double patenting over claims 23, 38, 39, 45-62 and 64 of copending Application No. US Publication No. 20040208856 ('856). **This rejection is withdrawn** because the claims of '856 have issued and are drawn specifically to methods of treating hyperlipidemia, delaying the onset of hyperlipidemia, lowering cholesterol, and lowering serum and plasma triglyceride levels in an animal, while the methods of the instant invention are drawn specifically to methods of ameliorating hepatic steatosis and lowering liver triglyceride levels in an animal.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed May 14, 2008, claims 61, 65-70, 72-76, and

84-99 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shachter, N. (Applicant's Reference BF on the Information Disclosure Statement filed August 14, 2007), in view of GenBank Accession No. NT_035088 (Applicant's Reference BL on the Information Disclosure Statement filed August 14, 2007), Jong et al. (Arterioscler Thromb Vasc Biol., 1999 Vol. 19:472-484), Senior, K. (Drug Discovery Today, 2002 vol. 7:840-841, Applicant's Reference BE on the Information Disclosure Statement filed August 14, 2007), and Monia et al. (Applicant's Reference AE on the Information Disclosure Statement filed August 14, 2007). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed May 14, 2008.

Response to Arguments

In response to this rejection, Applicants, in their response filed November 14, 2008, argue that none of the cited references, whether considered alone or in combination teach or suggest that antisense inhibition of apolipoprotein C-III might result in amelioration of hepatic steatosis or reduction in liver triglyceride levels in an animal. More specifically, Applicants argue that both Shachter and Jong conclude that reduction of apolipoprotein C-III expression causes reduced *plasma* triglyceride levels, but mentions nothing regarding *liver* triglyceride levels. Applicants argue that nowhere is there any suggestion that hepatic triglyceride levels should necessarily follow plasma triglyceride levels. In fact, during a telephonic interview made of record June 15, 2009, Applicants contended that it is accepted in the art that a reduction in plasma triglyceride levels usually does not correlate to a decrease in liver triglyceride levels.

It should be noted that during the telephonic interview made of record June 15, 2009, the Examiner stated on the record that She will try to find specific references that correlate plasma triglyceride levels with liver triglyceride levels. The Examiner has found at least three references that correlate plasma triglyceride levels with liver triglyceride levels. These references have been made of record and incorporated into the instant rejection. The references will be discussed at length below.

Applicant's specification at page 4, lines 16-27 discloses:

> "The hypolipidemic effect of the fibrate class of drugs has been postulated to occur via a mechanism where peroxisome proliferator activated receptor (PPAR) mediates the displacement of HNF-4 from the apolipoprotein C-III promoter, resulting in transcriptional suppression of apolipoprotein C-III… The statin class of hypolipidemic drugs also lower triglyceride levels via an unknown mechanism, which results in increases in lipoprotein lipase mRNA and a decrease in plasma levels of apolipoprotein C-III..."

Roglans et al. (Journal of Pharmacology and Experimental Therapeutics, 2002 Vol. 302:232-239) teaches that atorvastatin, a well-established member of the statin class, markedly reduced plasma triglyceride levels and reduced liver triglyceride content in fructose-fed rats. See Table 2 and Figure 3B, respectively.

Funatsu et al. (Biochimica et Biophysica Acta, 2002 Vol. 1580 :161-160) teach that atorvastatin decreases hepatic triglyceride synthesis activity, and this activity was correlated with both hepatic and plasma triglyceride concentration (see Abstract, Figure 4A, and Figure 4B). More specifically, Funatsu et al. teach that the hepatic triglyceride synthesis activity correlated significantly with both the hepatic triglyceride concentration and plasma triglyceride concentration (see page 169, first column). Funatsu et al. conclude that their findings suggest that a reduction in triglyceride synthesis decreases

hepatic triglyceride concentration, which in turn decreases plasma triglyceride concentration (see page 169, first column).

To further underscore the relationship between plasma triglyceride levels and hepatic tissue triglyceride levels, Ugawa et al. (British Journal of Pharmacology, 2003 Vol. 139:140-146) teaches that YM-53601, a squalene synthase inhibitor, which shares some characteristics with the fibrate class of drugs, reduces plasma triglyceride levels in rodents (see Abstract, for example). Ugawa et al. teach that YM-53601 decreases plasma triglyceride levels in rats (see Figure 1) and this correlates to a parallel decrease of liver triglyceride levels (see Figure 2).

Given these teachings, contrary to Applicant's assertions, there is a suggestion in the art that hepatic triglyceride levels necessarily follow plasma triglyceride levels, and vice versa. Furthermore, and despite Applicant's assertions, it is accepted in the art that a reduction in plasma triglyceride levels usually correlates to a decrease in liver triglyceride levels, and vice versa.

Thus, one of ordinary skill in the art would believe that reduction in plasma triglyceride levels as concluded by Shachter and Jong would correlate to a reduction in liver triglyceride levels, as evidenced by Roglans et al., Funatsu et al. and Ugawa et al. Furthermore, a reduction in liver triglyceride levels would susequently ameliorate hepatic steatosis since the accumulation of lipids is decreased in hepatic tissue.

In view of the foregoing, when all the evidence is considered, the totality of the rebuttal evidence of non-obviousness fails to outweigh the evidence of obviousness made of record. Thus, it is maintained that the invention as a whole would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
August 11, 2009